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Michael O. Leavitt, Administrator
U.S. Environmental Protection Agency
Ariel Rios Bldg. (1101A)
1200 Pennsylvania Ave. NW
Washington, DC 20460



PETA

PEOPLE FOR THE ETHICAL
TREATMENT OF ANIMALS

HEADQUARTERS
501 FRONT STREET
NORFOLK, VA 23510
TEL 757-622-PETA
FAX 757-622-0457

Comments on the HPV test plan for the pyridine and pyridine derivatives category

Dear Administrator Leavitt:

The following comments on the test plan for pyridine and pyridine derivatives, prepared by the American Chemistry Council (ACC), are submitted on behalf of People for the Ethical Treatment of Animals, the Physicians Committee for Responsible Medicine, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These animal, health, and environmental protection organizations have a combined membership of more than ten million Americans.

The ACC plans to carry out two reproductive and developmental toxicity tests (OECD test guideline 421) on pyridine and nicotinotrile. The ACC has prepared a test plan that covers seven compounds and two groups of compounds and has provided an enormous database for these chemicals (a 500+ page robust summary document that includes at least 16 acute oral toxicity mammalian studies; 11 acute inhalation mammalian studies; 13 acute dermal mammalian studies; 16 repeated-dose mammalian studies including reproductive endpoints; 40 *in vitro* genetic toxicity studies; 5 *in vivo* genetic toxicity studies; and one developmental toxicity study). Given the huge wealth of information that exists on these substances, the additional testing proposed is all the more inexplicable.

Further, the ACC presents existing developmental toxicity data that it considers adequate for one member of the category, pyridine (p. 384 of the robust summary). In addition, both histopathological examinations of the reproductive organs and spermatogenesis were analyzed in repeated-dose studies (p. 15 of the test plan). Given these data, the negative genetic toxicity data, and the extensive body of knowledge on these chemicals (including NTP carcinogenicity studies on two species of animals for pyridine), it is difficult to fathom why the ACC is proposing to conduct more toxicity testing on yet another 1,350 animals. The October 1999 letter to HPV participants specifically states that "In analyzing the adequacy of existing data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach. Participants may conclude that there is sufficient data, given the totality of what is known about a chemical, including human experience, that certain endpoints need not be tested." Yet the ACC, once again, is clearly disregarding this important principle. Surely substances with such an extensive database are not the chemicals that EPA and Environmental Defense had in mind when they claimed there was a "vacuum of information" on HPV chemicals that needed to be filled through additional testing in the HPV chemical-testing program.

Even attempting to follow the ACC's reasoning in wanting additional testing performed for this category and realizing that piperidine is the category member most unlike the others in that it does not contain the pyridine ring, it is still unclear why (1) piperidine data cannot be read across to other compounds and (2) why developmental toxicity tests are required for both pyridine and nicotinitrile and why one test would not suffice. It may be the case that the ACC judges that data from pyridine can be read across to hydrocarbon-substituted pyridines [2-, 3-, and 4-picoline, pyridine alkyl derivatives, and pyridinium 1-(phenylmethyl)-Et Me derivative chlorides], but not to nitrile-substituted pyridines (nicotinonitrile and picolinonitrile). If this is in fact the case, we would then like to know if the ACC has attempted to estimate the toxicological effects of nitrile substitution on the basis of the known toxicity of other nitriles. The ACC's reasoning with respect to the category should be explained more thoroughly, and a serious attempt should be made to estimate developmental toxicity on the basis of existing data and structure-activity relationships.

To summarize, there is much the ACC could have done with the massive amount of data that already exist on these substances to apply thoughtful toxicology. It has failed once again to do so.

If the ACC insists on the necessity of a reproductive and developmental toxicity tests, we request that it perform the rodent embryonic stem cell test (EST). This *in vitro* embryotoxicity method has been validated by the European Centre for the Validation of Alternative Methods (ECVAM), and the Centre's Scientific Advisory Committee has concluded that the test is ready to be considered for regulatory purposes (Genschow 2002). We have repeatedly provided validation and SOP references, and we have suggested that, in the HPV *screening-level* program, a positive EST results should warrant the substance's treatment as a developmental toxicant, so that no further testing should be carried out under the HPV program.

Even if the ACC decides to carry out OECD test 421, we urge it to consider performing the EST in parallel. Several companies are considering this option in order to help build a database for industrial chemicals, for eventual validation of the EST in the U.S. We are currently awaiting a response from the ACC to a written request on this issue. .

I would appreciate receiving a response to the specific issues raised in these comments from both the EPA and the ACC. I can be reached at 757-622-7382, ext. 8001, or via e-mail at JessicaS@peta.org.

Sincerely,

Jessica Sandler
Federal Agency Liaison

References

Genschow, E., "The ECVAM international validation study on *in vitro* embryotoxicity tests: Results of the definitive phase and evaluation of prediction models", *Alternatives to Laboratory Animals* 30: 151-176, 2002.